REMARKS

The Office Action of October 16, 2002 has been reviewed and the Examiner's comments carefully considered.

Claims 7-14 are presently pending in the application. Claims 8-11 have been withdrawn from consideration as being drawn to a nonelected invention. The present Amendment submits a replacement Information Disclosure Statement identical to the Information Disclosure Statement filed August 31, 2001, corrects the brief description of Figure 2 to refer to parts A and B, amends Claim 7, cancels claims 8-11, and adds claim 15 in accordance with the originally filed application. Support for claim 7 is found on page 4, lines 1-9 and Example 4. Support for claim 15 is found in Example 1, subsection 2.5. No new matter has been added.

In reviewing the Examiner's comment that "the Information Disclosure Statement fails to comply with 37 C.F.R. 1.97, 1.98 and MPEP § 609 because it is not present with the application," Applicants understand that the Information Disclosure Statement became detached from the above-identified patent application somewhere in the United States Patent and Trademark Office, or was never matched up with the file, notwithstanding Applicants' earlier submission of it. If Applicants' understanding is incorrect, Applicants would appreciate clarification. In any case, submitted herewith as requested is a complete copy of the Information Disclosure Statement filed on August 29, 2001, together with a copy of the postcard date-stamped by the U.S. Patent Office acknowledging receipt.

Claims 7 and 12-14 stand rejected under 35 U.S.C. 112, first paragraph for assertedly not reasonably providing enablement for mini-plasmin, micro-plasmin, neutralizing compounds with the catalytic domain of plasmin, mutants and hybrids thereof.

Applicants respectfully traverse this rejection by pointing out that the new and unexpected feature of the claimed invention is the recognition that the administration of α2-antiplasmin neutralizing agents significantly decreases the size of cerebral ischemic infarcts. Thus, once it is appreciated that the goal is to neutralize α2-antiplasmin activity *in vivo*, those skilled in the art would have little difficulty identifying or obtaining the various α2-antiplasmin neutralizing compounds known to exhibit such action within a reasonable number of attempts. For example, it is well known in the art that molecules such as microplasmin having the active catalytic domain of plasmin can be obtained by a high alkaline autolytic reaction of plasmin and plasminogen. Alternatively, microplasmin or miniplasmin can be generated by a plasminogen activator such as streptokinase or staphylokinase.

Claims 7 and 12-14 stand rejected under 35 U.S.C. 112, second paragraph for assertedly failing to specify to whom or what the recited compounds should be administered. Claim 7 has been amended to recite that treatment is administered to animals or patients. Thus, amended claim 7, and dependent claims 12-14, are now complete.

Claims 7 and 12-14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al. Applicants traverse this rejection by asserting that Eibl's disclosure of using a pharmaceutical composition of lys-plasminogen and plasmin for preventing ischemia as well as treating reperfusion injury subsequent to a stroke does not anticipate the use of compounds, such as plasmin, mini-plasmin, micro-plasmin and monoclonal antibodies, to neutralize α2-antiplasmin so as to significantly reduce the size of cerebral infarcts after the occurrence of a cerebral ischemic attack. In particular, preventing an ischemic attack necessarily occurs before the onset of a cerebral ischemic infarct, and reperfusion injury occurs after an infarct is degraded and blood flow to the surrounding tissue (penumbra) is restored, such injury due to the reentry

of oxygen or other substances into the area, which kills off or further injures portions of the injured tissue. Thus, Eibl's addressing of treatment prevention and reperfusion injury focuses on events occurring prior to or subsequent to a cerebral ischemic infarction, whereas the claimed invention treats the infarction *per se*. Furthermore, Eibl teaches the use of a pharmaceutical composition of lys-plasminogen and plasmin to treat these events. Lys-plasminogen is an inactive precursor molecule of plasmin, and does not have the active catalytic domain of plasmin. Thus, lys-plasminogen has a low affinity for α2-antiplasmin binding. That is to say, although lys-plasminogen binds to α2-antiplasmin with low affinity and thus is capable of competitively inhibiting α2-antiplasmin's binding to its natural substrate, plasmin, it is not the preferred substrate for α2-antiplasmin and thus is incapable of neutralizing α2-antiplasmin, i.e., completely blocking its activity *in vivo*. In contrast, the claimed invention specifically requires the administration of compounds that effectively neutralize α2-antiplasmin, rather than compounds that merely inhibit their action.

Therefore, the new and unexpected feature of the present invention inheres in the discovery that focal cerebral ischemic infarcts are significantly reduced in size by administering to an animal or patient compounds that neutralize, rather than merely inhibit, α2-antiplasmin. Eibl neither teaches nor suggests administering α2-antiplasmin neutralizing compounds to animals or patients that have experienced a cerebral ischemic infarction in order to significantly decrease the size of the infarct. In fact, Eibl teaches away from administering neutralizing agents by disclosing the use of pharmaceutical compounds containing constituents that are known to not have a neutralizing effect on α2-antiplasmin, e.g., lys-plasminogen.

For all the foregoing reasons, claim 7 as amended, new claim 15, and claims 12-14 are patentable over the cited prior art and in condition for allowance. Reconsideration of the rejections and allowance of all pending claims 7 and 12-14 is respectfully requested.

Respectfully submitted,

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MARKED-UP VERSION OF CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 5, line 8 has been rewritten as follows:

Figure [2] 2A shows the effect of adenoviral transfer of the t-PA [or PAI-1 genes] gene on focal ischemic cerebral infarct size in t-PA [or PAI-1] deficient mice.

Figure 2B shows the effect of adenoviral transfer of the PAI-1 gene on focal ischemic cerebral infarct size in PAI-1 deficient mice.

IN THE CLAIMS:

Claim 7 has been amended as follows:

7. (Twice Amended) A method for the treatment of focal cerebral ischemic infarction by administering to an animal or a patient at least one α2-antiplasmin neutralizing compound in an effective amount that significantly reduces the size of a cerebral ischemic infarct.

Claims 8-11 are canceled herein.

New claim 15 has been added as follows:

15. (New) The method of claim 14, wherein the at least one α2-antiplasmin neutralizing compound is administered intracranially.